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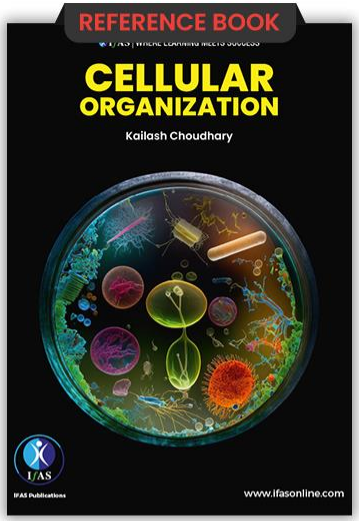
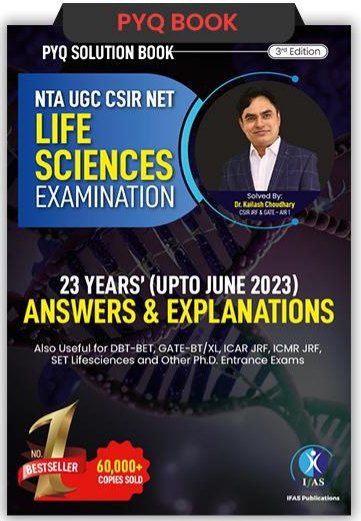
CSIR NET – Life Science

Unit 2: Cellular Organization

L8 Secretory pathway

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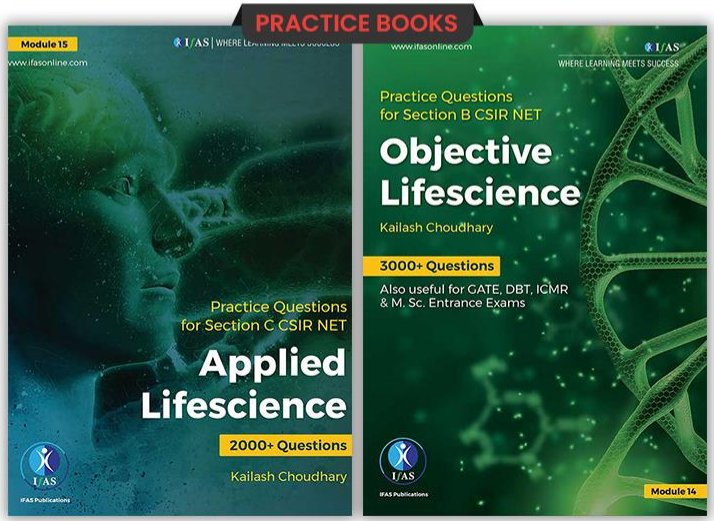

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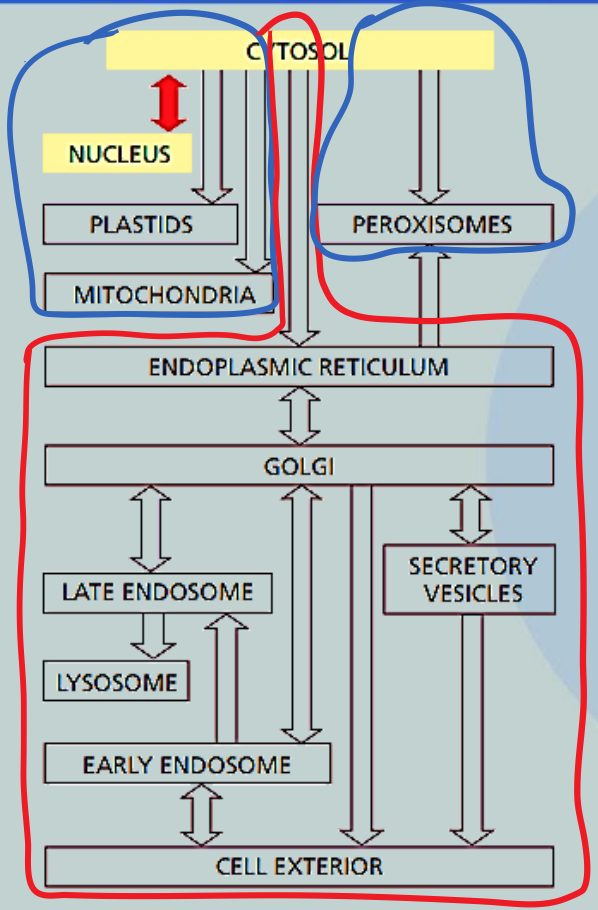
Secretory pathway

Points to be covered in this Lecture

- secretory pathway
- Retrograde, annograde pathway and coat protein
- Experimental approch for secretory pathways, signal sequance
- Protein targetting to ER
- Proten targetting to lysosome

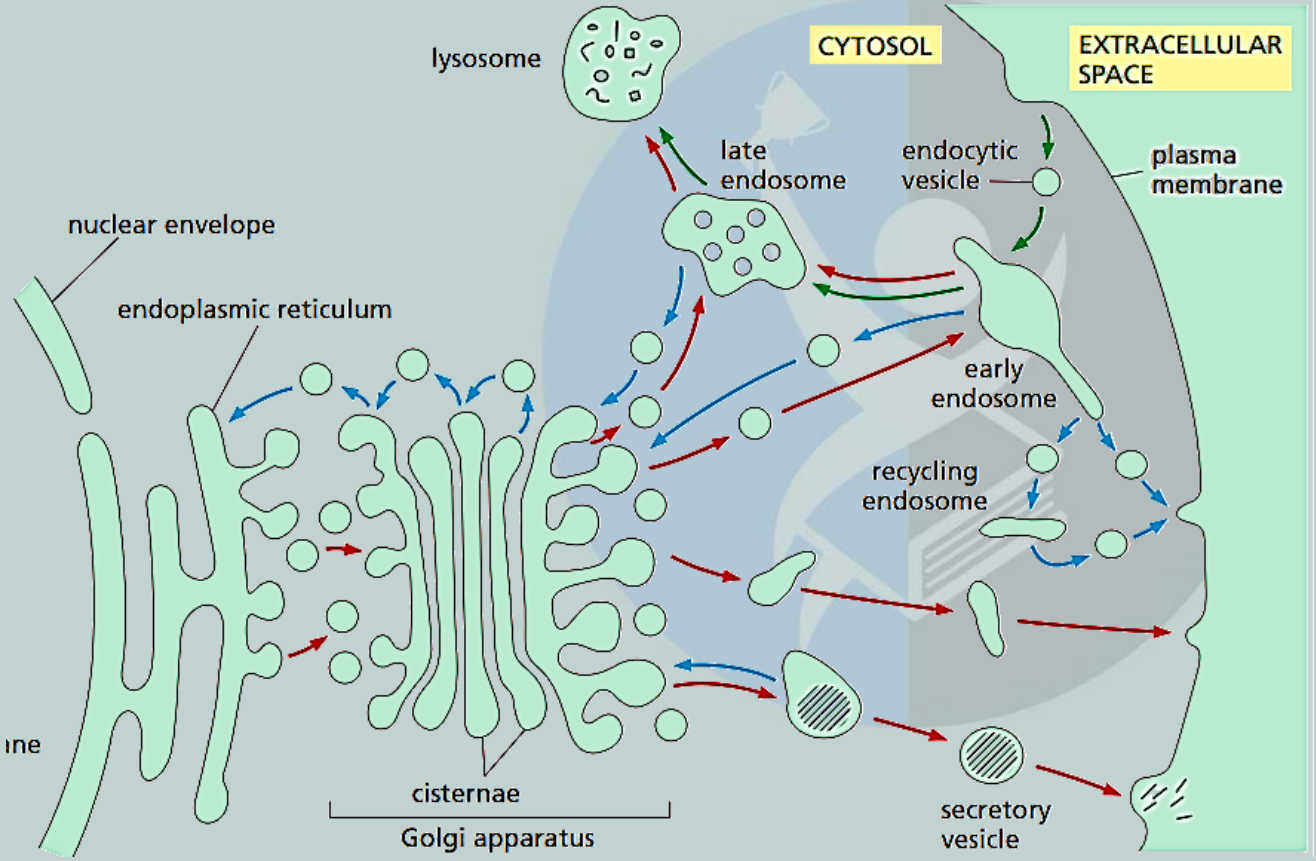
Secretory pathway



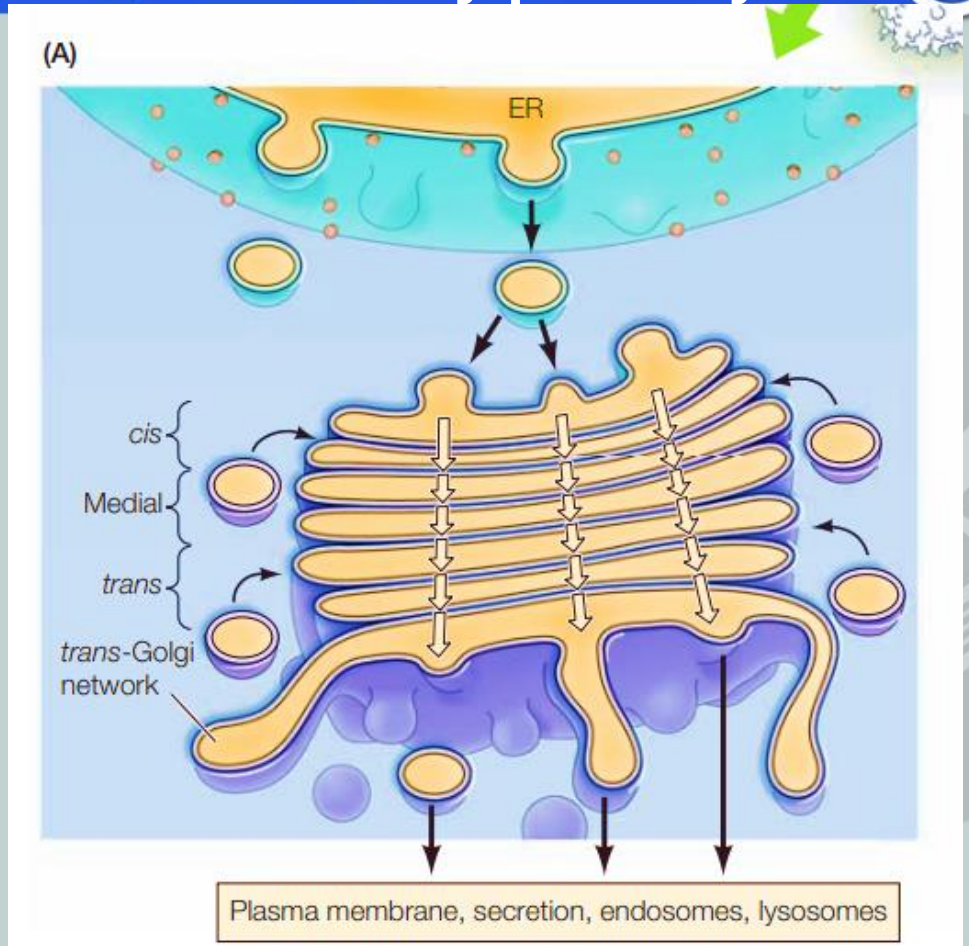
Cytosolic Protein

Secretory pathway

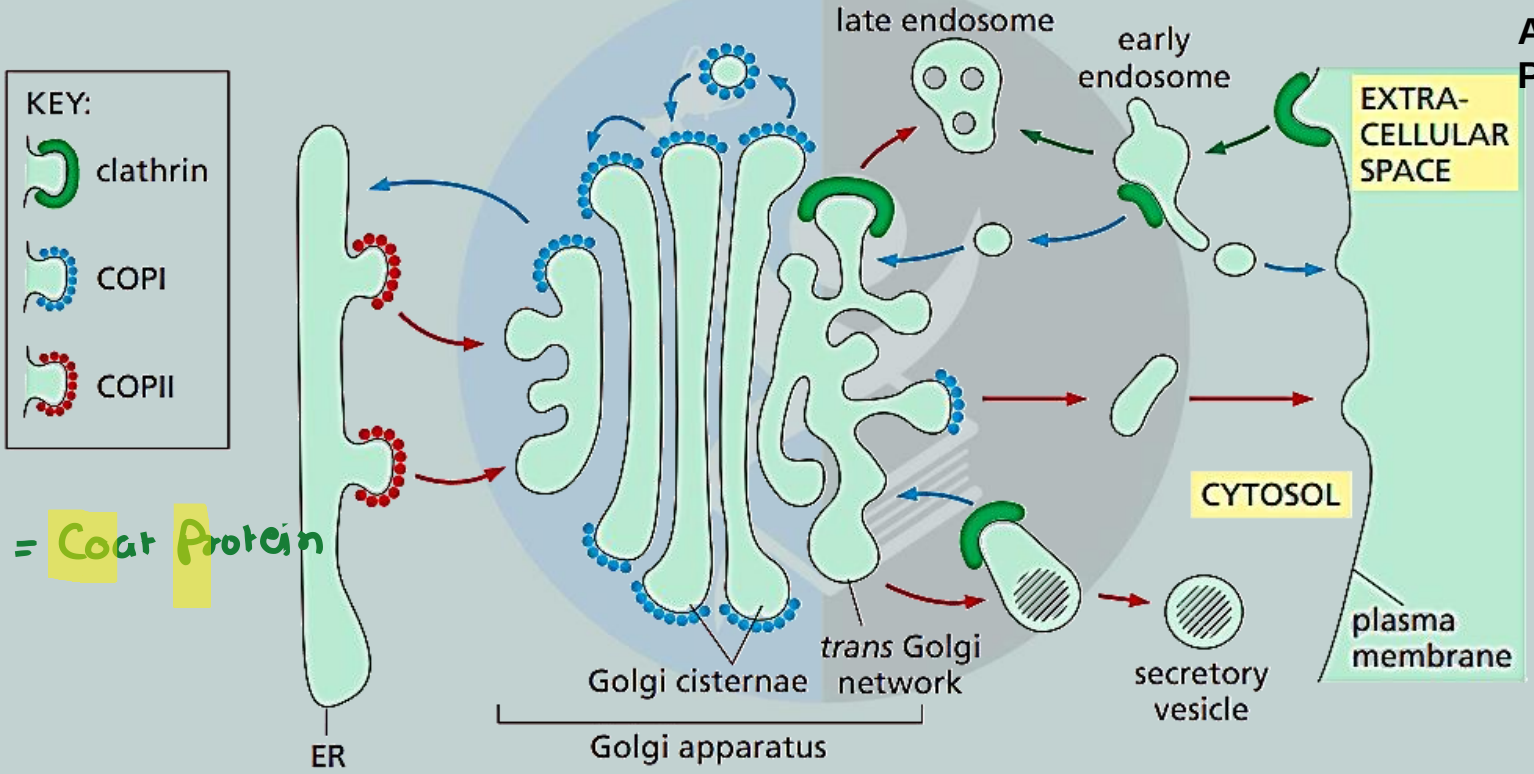
A “road-map” of the secretory and endocytic pathways.



Secretory pathway



Secretory pathway and ~~Coat Pro~~teins -> gmp ->



Annograde Path

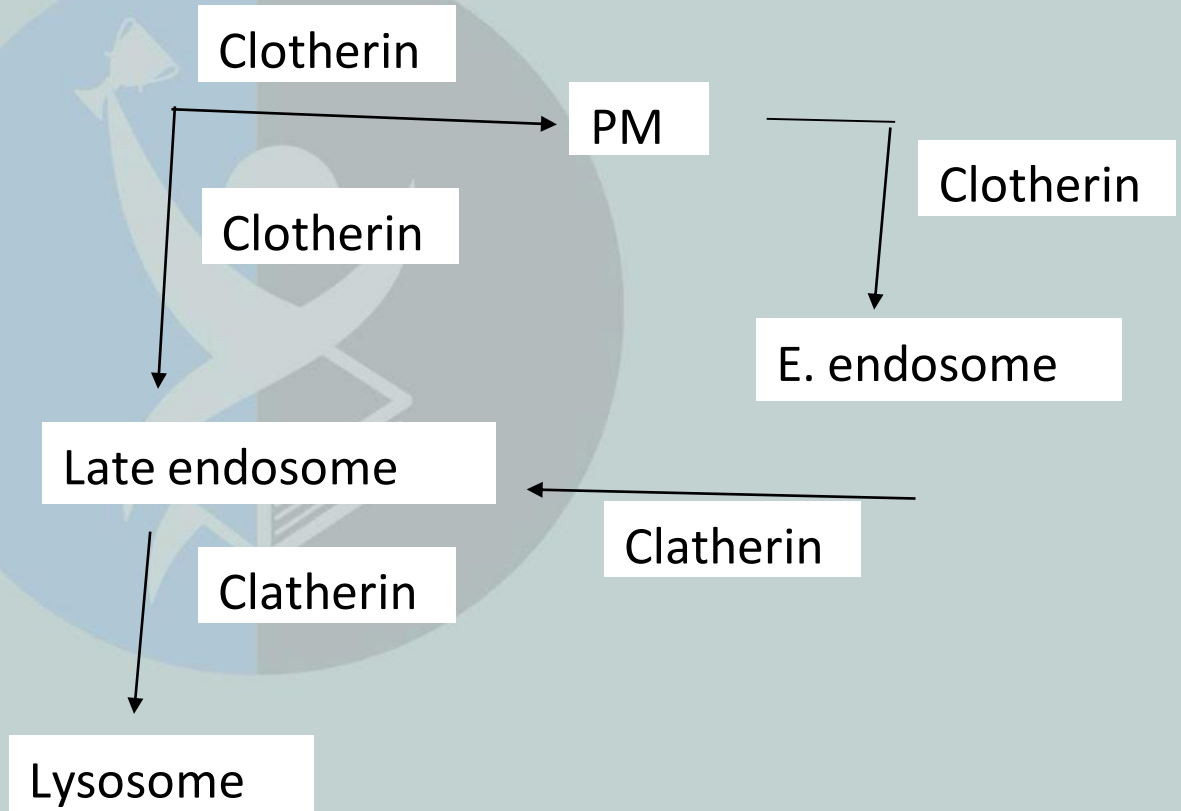
<- Retrograde Path

<- Endocytoht Path

Cop = Coat Protein

Annograde pathway

$$\text{RER} \xrightarrow[\text{Cop II}]{} Cis\ Golgi \xleftarrow[Cop\ I]{} Trans\ Golgi$$



Some adapter Protein and G Protein is required for Coat formation around vesicle.

Guanosine Triphosphatases That Regulate Membrane Traffic

G-Protein

Two major families of small guanosine triphosphatases (GTPases)—

1. Arf (adenosine diphosphate [ADP]-ribosylation factor) and
2. Rab (Ras-related in brain)

ADP-Ribosylation Factor and Sar1 GTPases

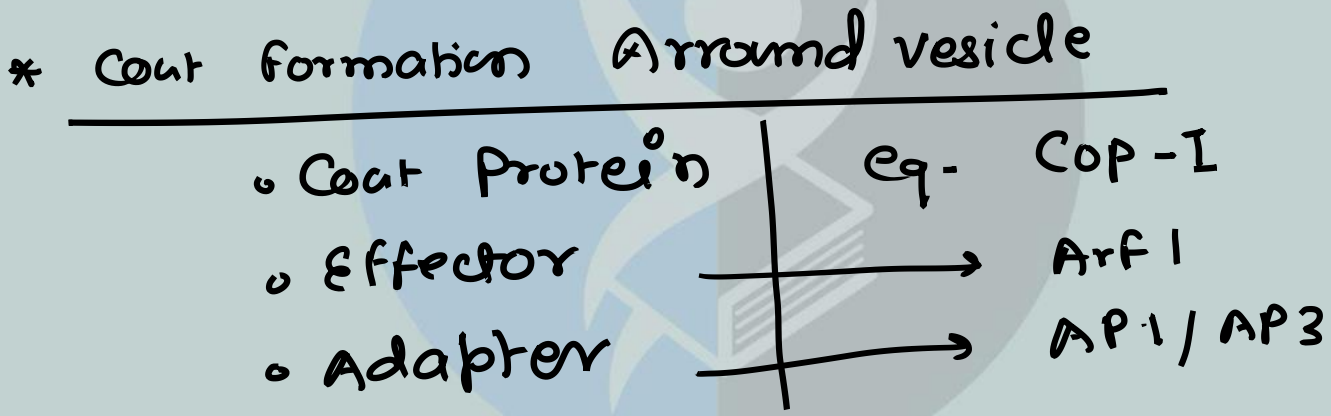
Arf family GTPases, including Arf1 to Arf6 and Sar1 (secretory and Ras-related) GTPase, recruit specific protein effectors to the membrane surface

Arf Family

- **Arf 1, 6**
- **Sarl**

- The toxic fungal metabolite brefeldin A----------| **ArF 1** inhibits Arf1 activation in the secretory pathway by trapping a Sec7 domain–Arf–GDP complex.
- This prevents Arf1 activation by GTP, blocks the secretory pathway and causes the Golgi apparatus to disassemble.

Arf1's effectors include the coat protein I (COPI) coat in the early secretory pathway; the adaptor protein 1 (AP1), and AP3 coats in post-Golgi trafficking



Annograde Path [ER → $Cis - Golgi$]

Cop – II + Sar- I- GTP

Cop – II

- Sec 23
- Sec 24
- Sec 13
- Sec 31

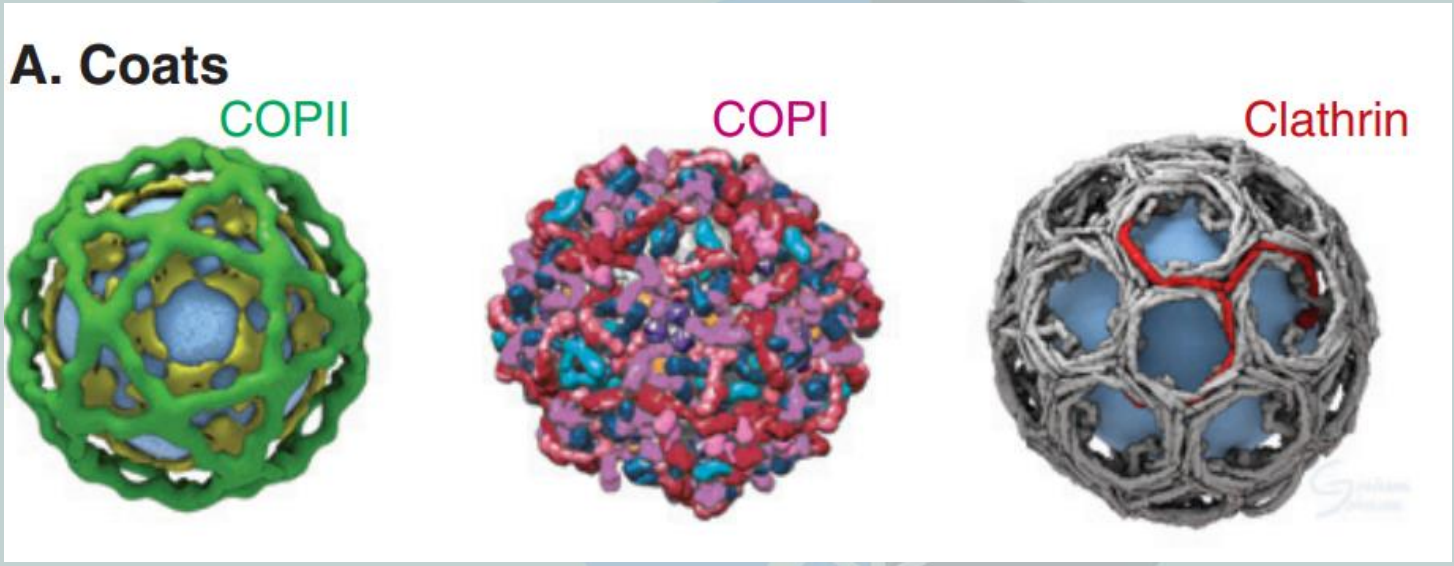
Sar- I- GTP – Small G – Protein

Sar-1- GTP

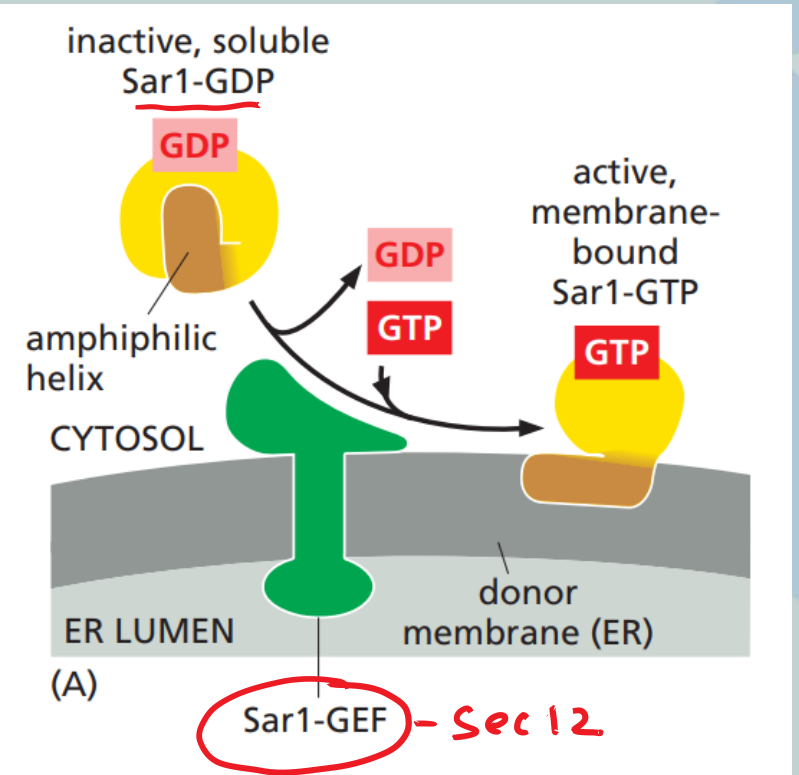
- insolube
- Vesicular formation

Sar 1-GDP

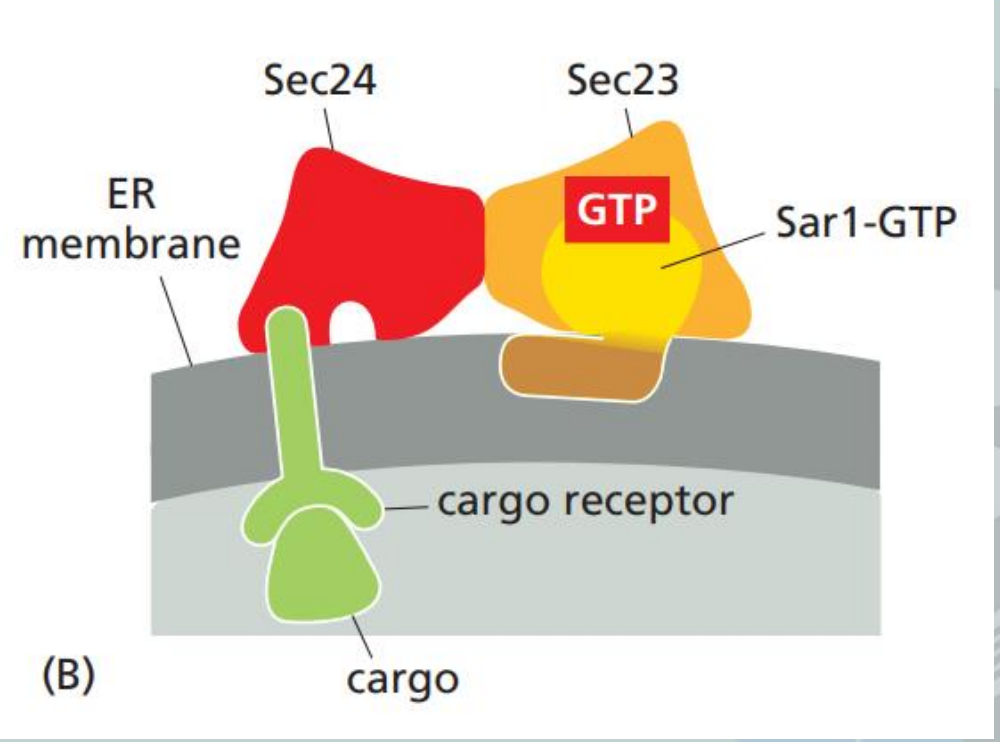
- Solubel
- Cop II coat removed


A. Coats
COPII
COPI
Clathrin

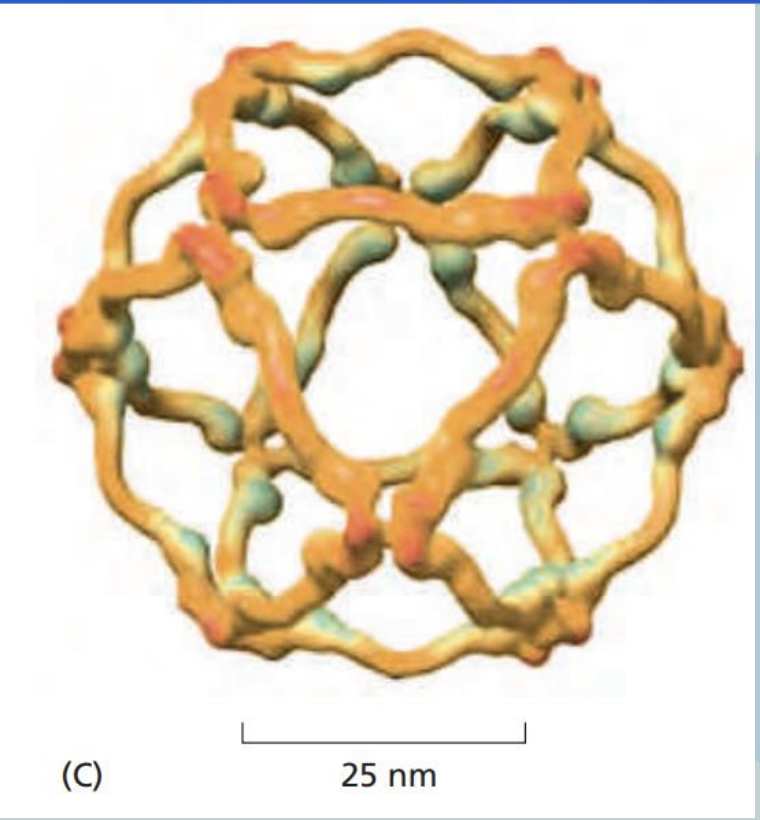
Formation of a COPIIcoated vesicle



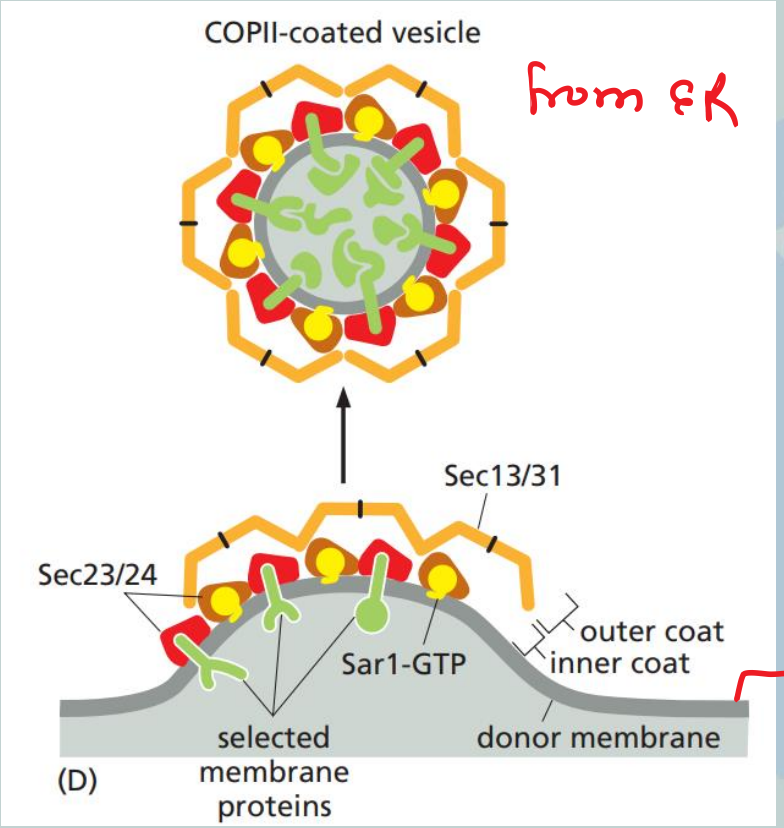
. (A) Inactive, soluble Sar1-GDP binds to a Sar1-GEF in the ER membrane, causing the Sar1 to release its GDP and bind GTP. A GTP-triggered conformational change in Sar1 exposes an amphiphilic helix, which inserts into the cytoplasmic leaflet of the ER membrane, initiating membrane bending (which is not shown)



(B) GTP-bound Sar1 binds to a complex of two COPII adaptor coat proteins, called Sec23 and Sec24.

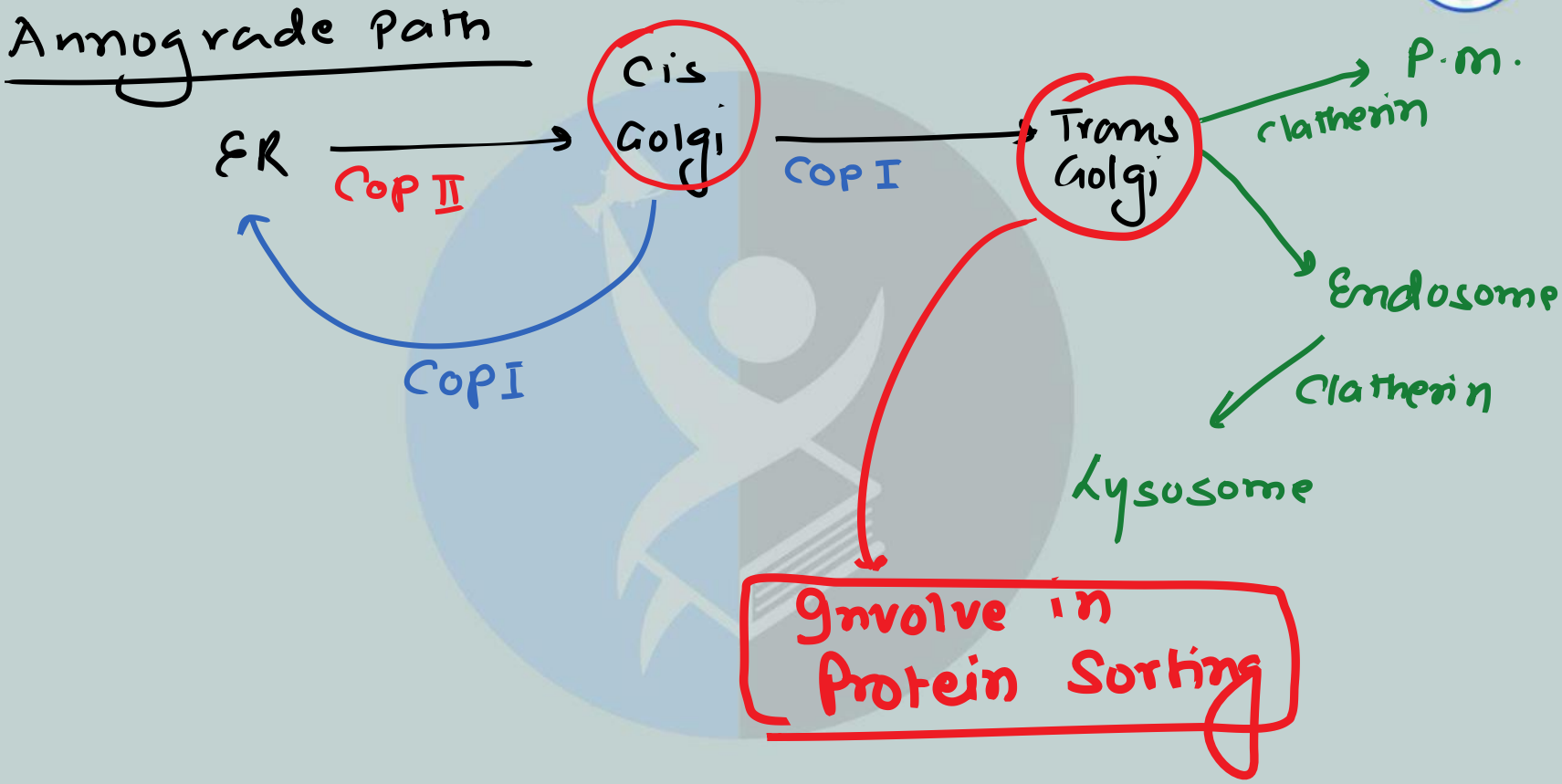


A complex of two additional COPII coat proteins, called Sec13 and Sec 31, forms the outer shell of the coat. Like clathrin,



Membrane-bound, active Sar1-GTP recruits COPII adaptor proteins to the membrane.

→ cis-Golgi


Anmograde Path
ER
Cis Golgi
Trans Golgi
P.M.
Clatherin
Endosome
Clatherin
Lysosome
COP II
COP I
COPI
Involve in Protein Sorting

Protein Sorting is Based upon- address/ signal on cargo Protein

Secretory pathway

Cytosolic Protein	
Nuclear Localization Signal (NLS) for nuclear targeting	"P-K-K-K-R-K-V" sequence on folded protein
Nuclear Export Signal (NES)	"LxxxLxxLxL" hydrophobic sequence
Mitochondrial targeting signal for matrix	"MLRTPAPARG" sequence forming alpha helix
Peroxisomal targeting sequence (PTS) -1	C-terminal "SKL" sequence on folded protein
Chloroplast transit peptide	"MSTLSSVSSPAPVSA" sequence
Secretory Protein	
Signal peptide for entry into ER	N-terminal hydrophobic patch
ER retention signal	C-terminal "KDEL" Sequence
ER resident membrane protein	C-terminal "KKXX" sequence
Lysosomal targeting signal	Mannose 6 Phosphate
Plasma membrane	C-terminal "NPXY" on LDL protein

Signal for protein Targetting and sorting.

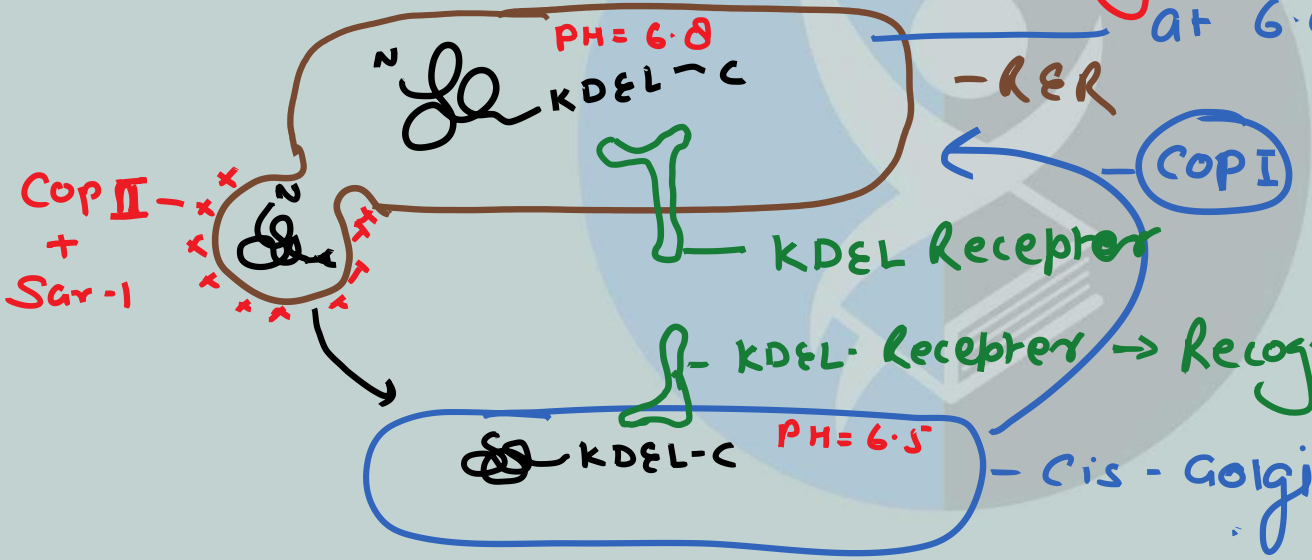
16-31 a.a.

→ Signal Recognized by cis Golgi

→ Recognized by Trans Golgi

Targetting of RER Luminal Protein

- KDEL Signal toward C Terminus



at 6.8 pH KDEL Dissociates from Receptor

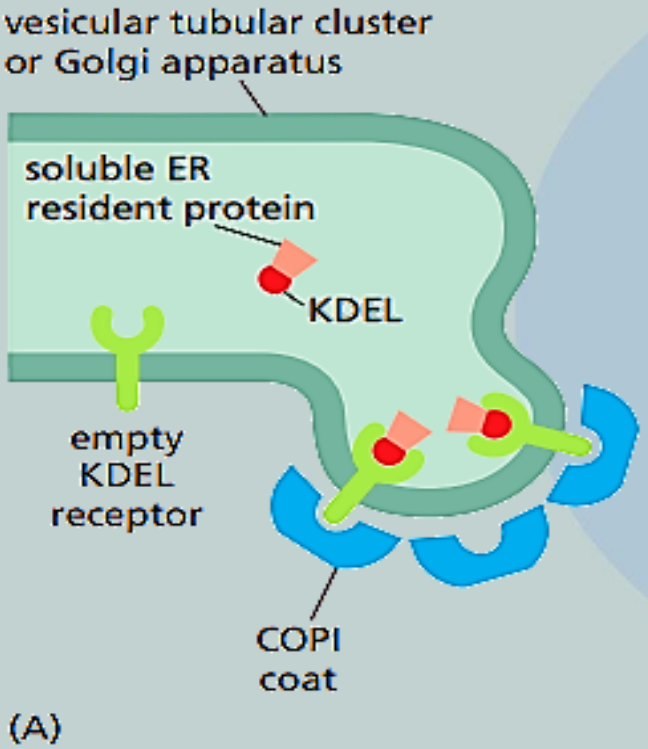
Targetting of RER Luminal Protein

KDEL Signal toward C Terminus at 6.8 PH KUEL Dissociates form Receptor

KDEL Receptor

KDEL – Receptor -> Recgnize KDEL Signal on RER Luminal

Cis Golgi Protein Binds with it



Targeting of RER Luminal Protein

KDEL Signal toward C Terminus

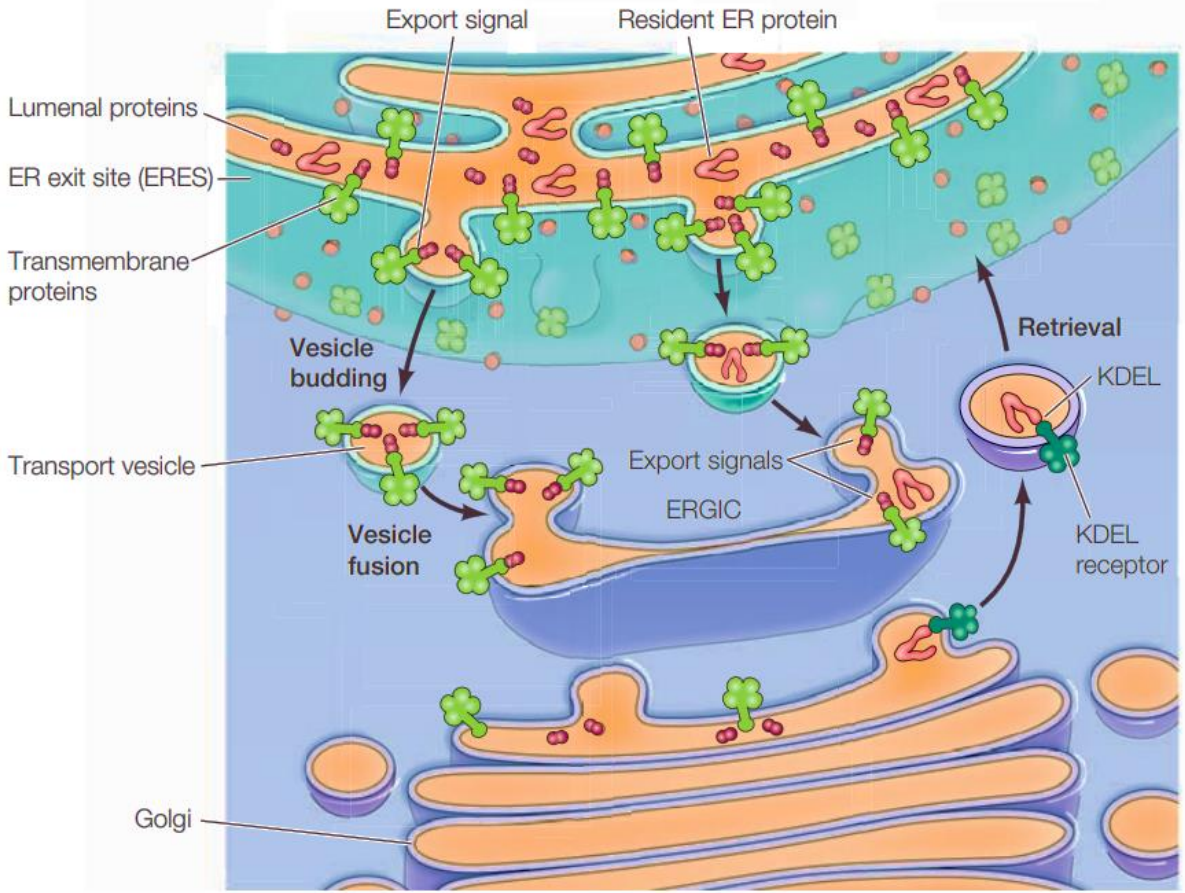
KDEL Dissociates form Receptor at 6.8 PH

KDEL Receptor

KDEL – Receptor -> Recognize KDEL Signal on RER Luminal

Cis Golgi Protein Binds with it

Secretory pathway



KDEL is necessary for protein targeting in RER

Necessity is confirmed by deletion of KDEL signal

If KDEL signal is deleted or mutated from RER protein

Proteins fails to target in RER lumen

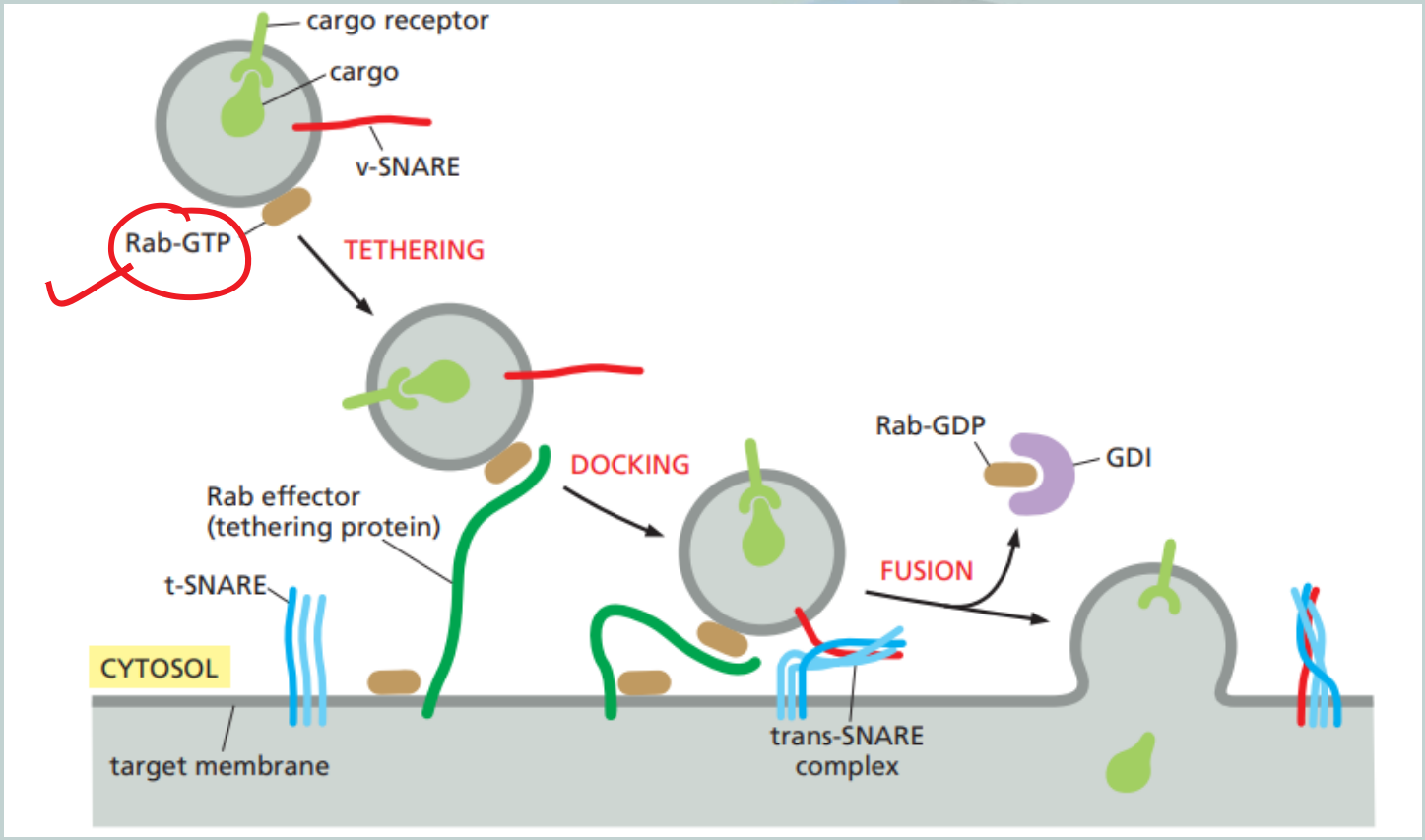
Without signal – Protein secreted out side from the Cell

If KDEL signal is added on any secretory protein

- Protein is target toward RER lumen
- KDEL –C is added on a Cytosolic protein
- This protein remain in the cytosol

Vesicular fusion during vesicular transport

Tethering of a transport vesicle to a target membrane



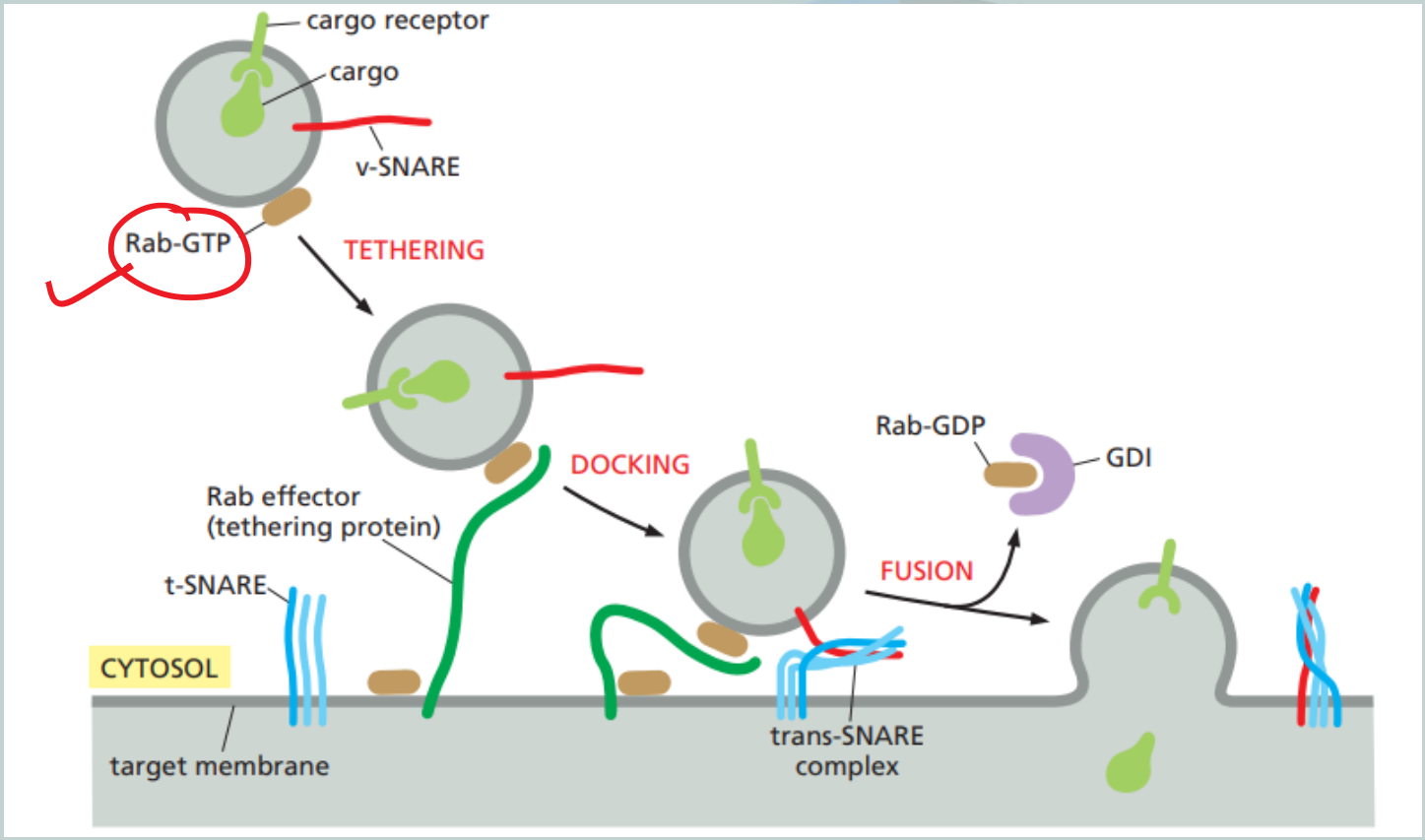
Rab GTPases

Rab family GTPases control protein–protein interactions between transport carriers and docking complexes on target membranes

Researchers use Rab proteins as markers for specific organelles (eg, Rab5 for early endosomes)

TABLE 13–1 Subcellular Locations of Some Rab Proteins	
Protein	Organelle
Rab1	ER and Golgi complex
Rab2	*cis* Golgi network
Rab3A	Synaptic vesicles, secretory vesicles
Rab4/Rab11	Recycling endosomes
Rab5	Early endosomes, plasma membrane, clathrin-coated vesicles
Rab6	Medial and *trans* Golgi
Rab7	Late endosomes
Rab8	Cilia
Rab9	Late endosomes, *trans* Golgi

Tethering of a transport vesicle to a target membrane



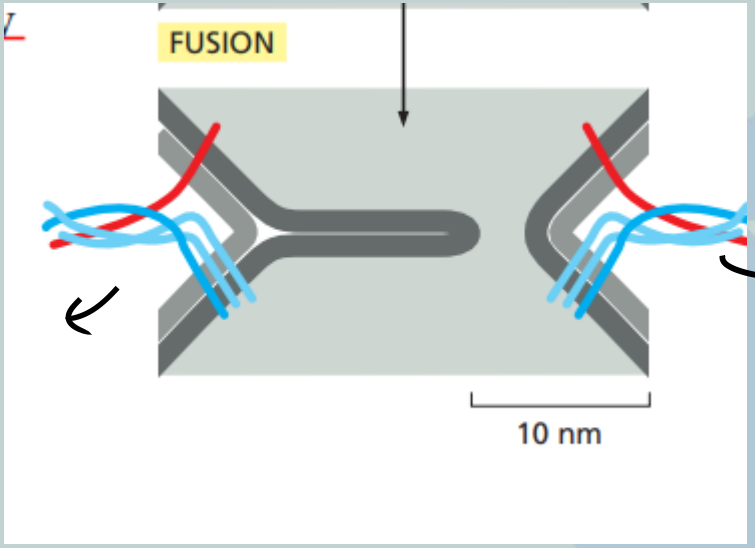
Tethering of a transport vesicle to a target membrane.

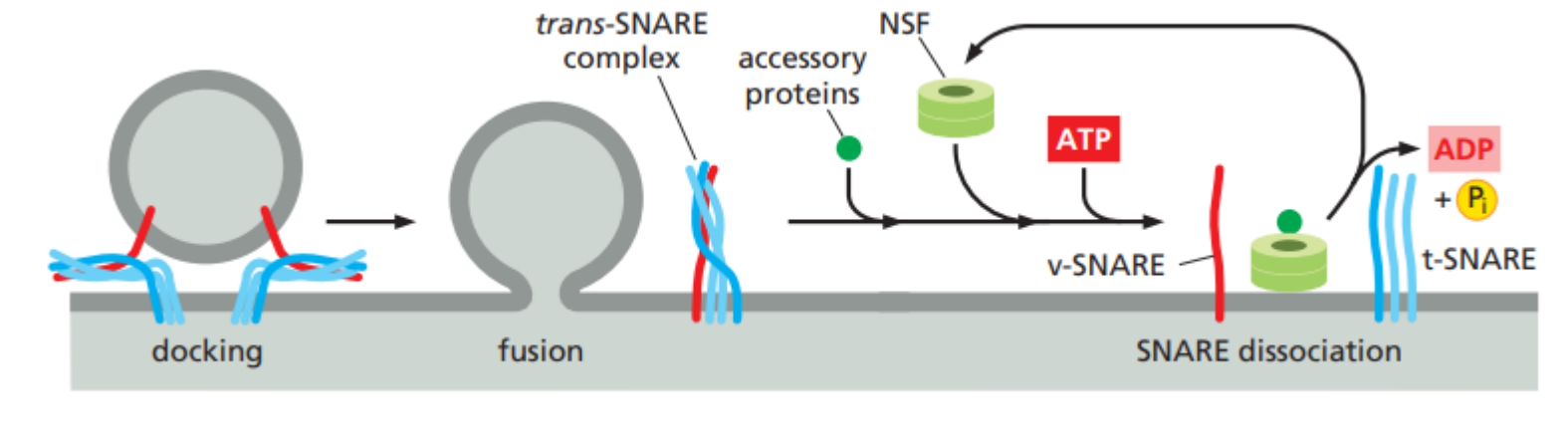
Rab effector proteins interact with active Rab proteins (Rab- GTPs, yellow) located on the target membrane, vesicle membrane, or both, to establish the first connection between the two membranes that are going to fuse. In the example shown here

- , the Rab effector is a filamentous tethering protein (dark green). Next, SNARE proteins on the two membranes (red and blue) pair, docking the vesicle to the target membrane and catalyzing the fusion of the two apposed lipid bilayers.

- During docking and fusion, a Rab-GAP (not shown) induces the Rab protein to hydrolyze its bound GTP to GDP, causing the Rab to dissociate from the membrane and return to the cytosol as Rab-GDP, where it is bound by a GDI protein that keeps the Rab soluble and inactive.

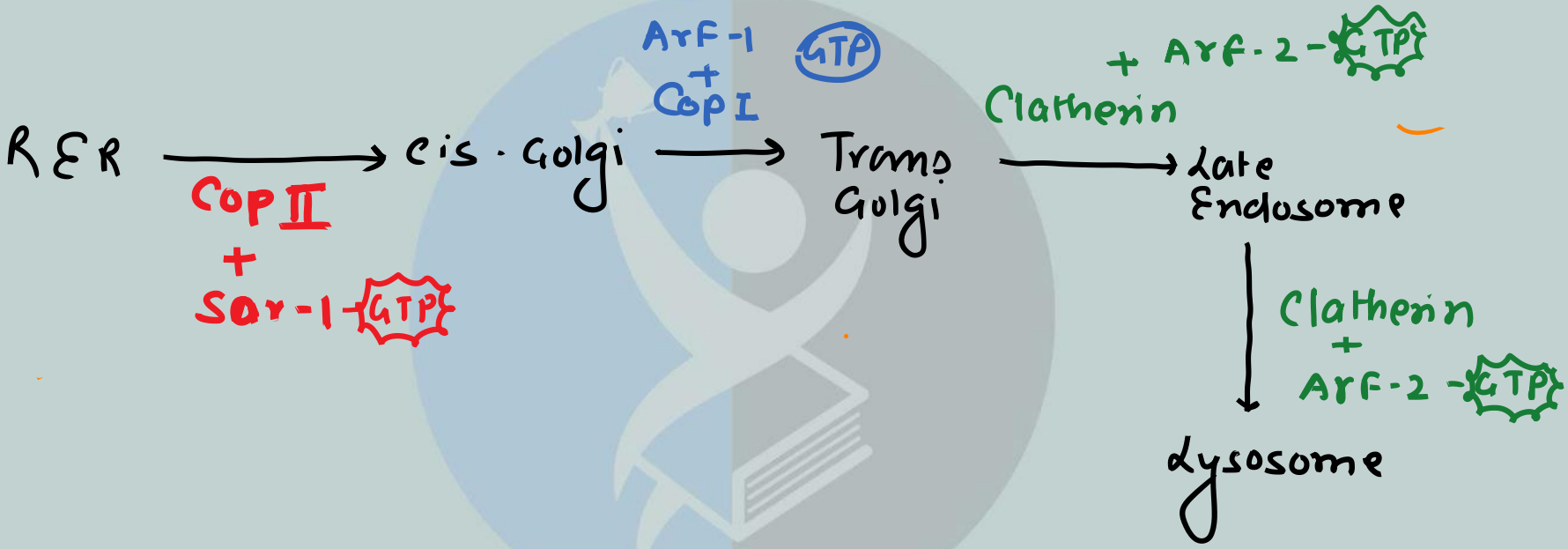
Secretory pathway





Dissociation of SNARE pairs by NSF after a membrane fusion cycle. After a v-SNARE and t-SNARE have mediated the fusion of a transport vesicle with a target membrane, NSF binds to the SNARE complex and, with the help of accessory proteins, hydrolyzes ATP to pry the SNAREs

Lysosomal protein targeting

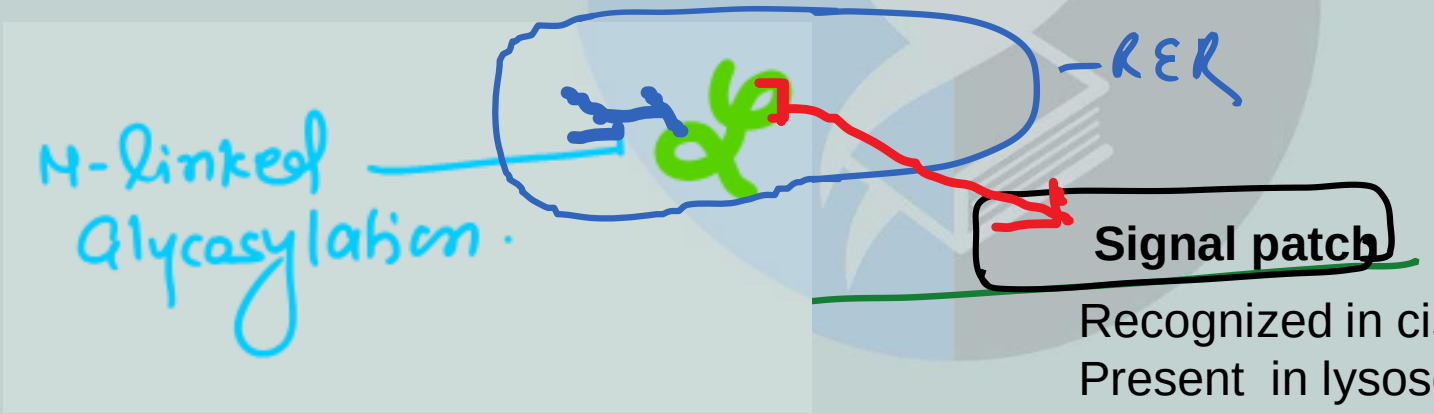


Lysosomal protein targeting

Targeting signal – Mannose –P

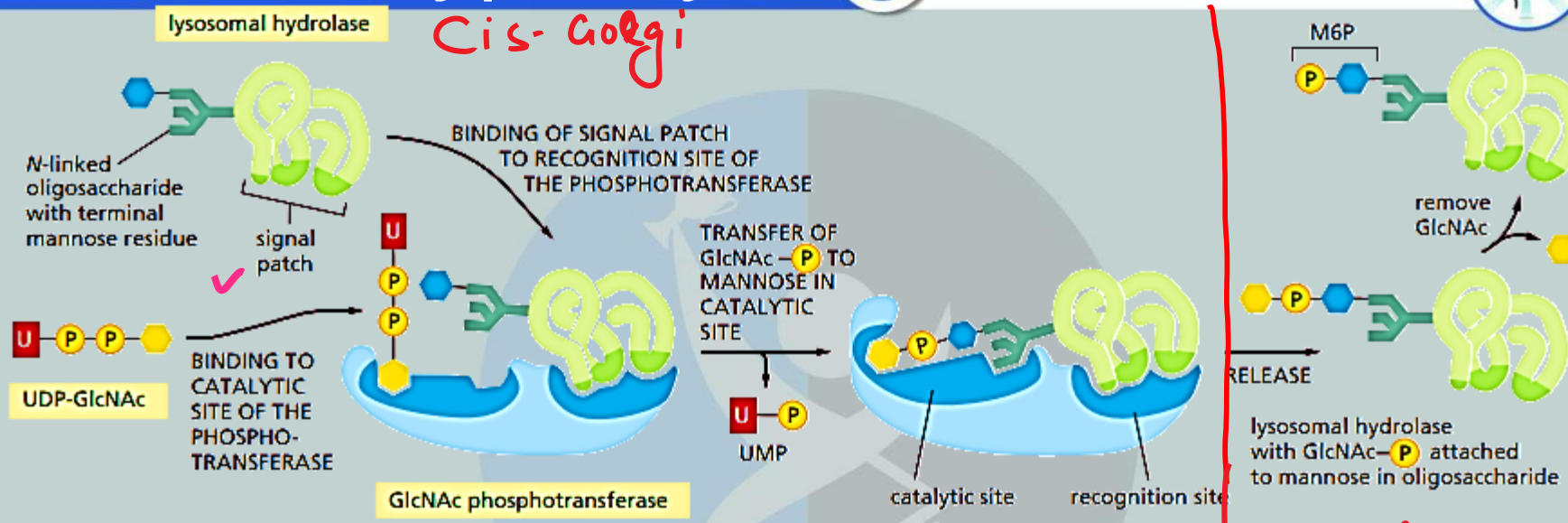
- Add in golgi
- Recognized in trans golgi

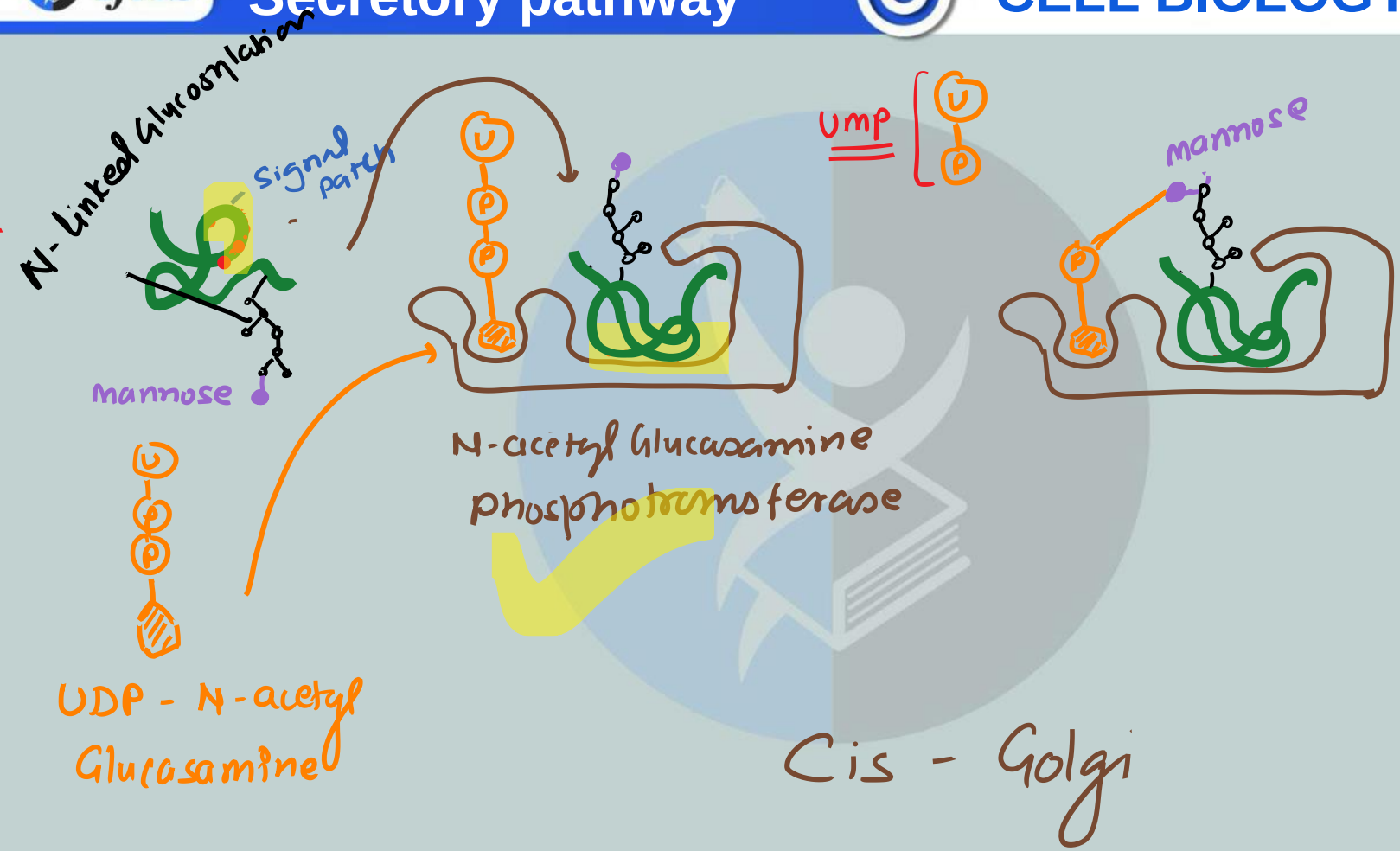
Protein synthesis occurs in RER

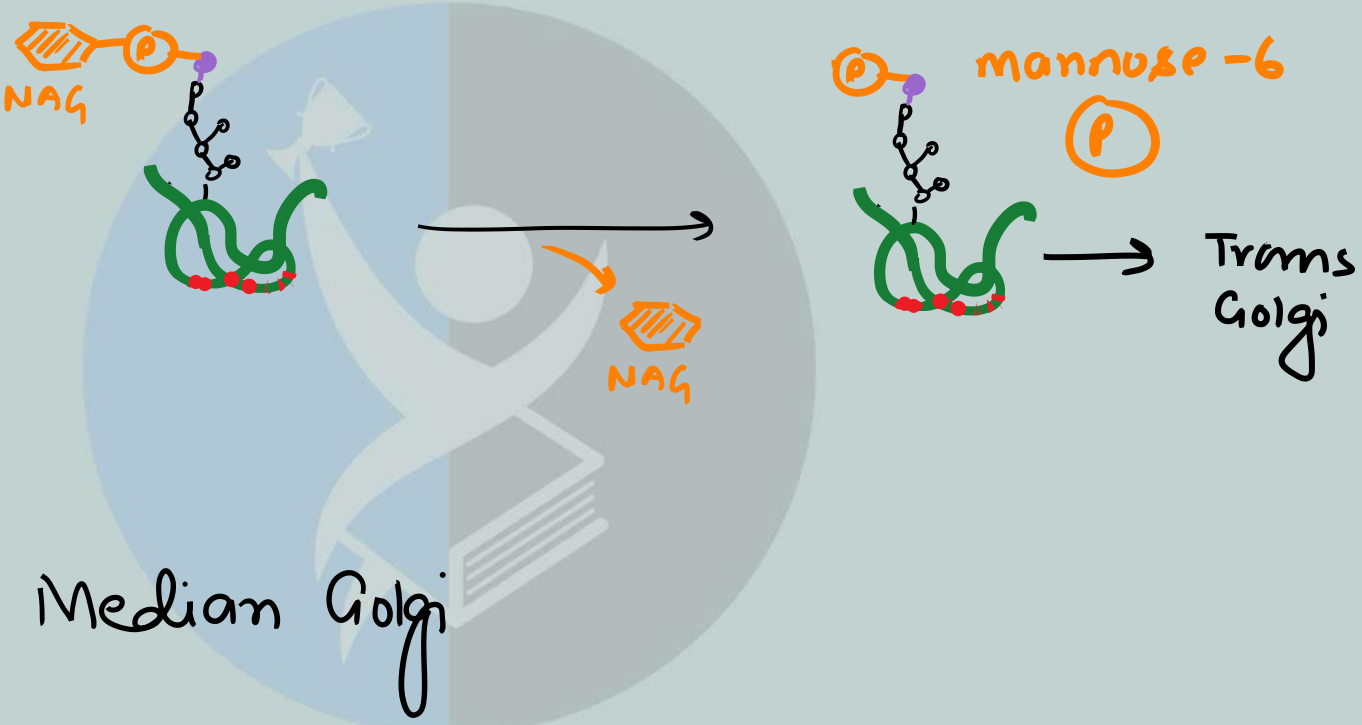


Recognized in cis - golgi
Present in lysosomal protein
Contain specific amino acid sequance

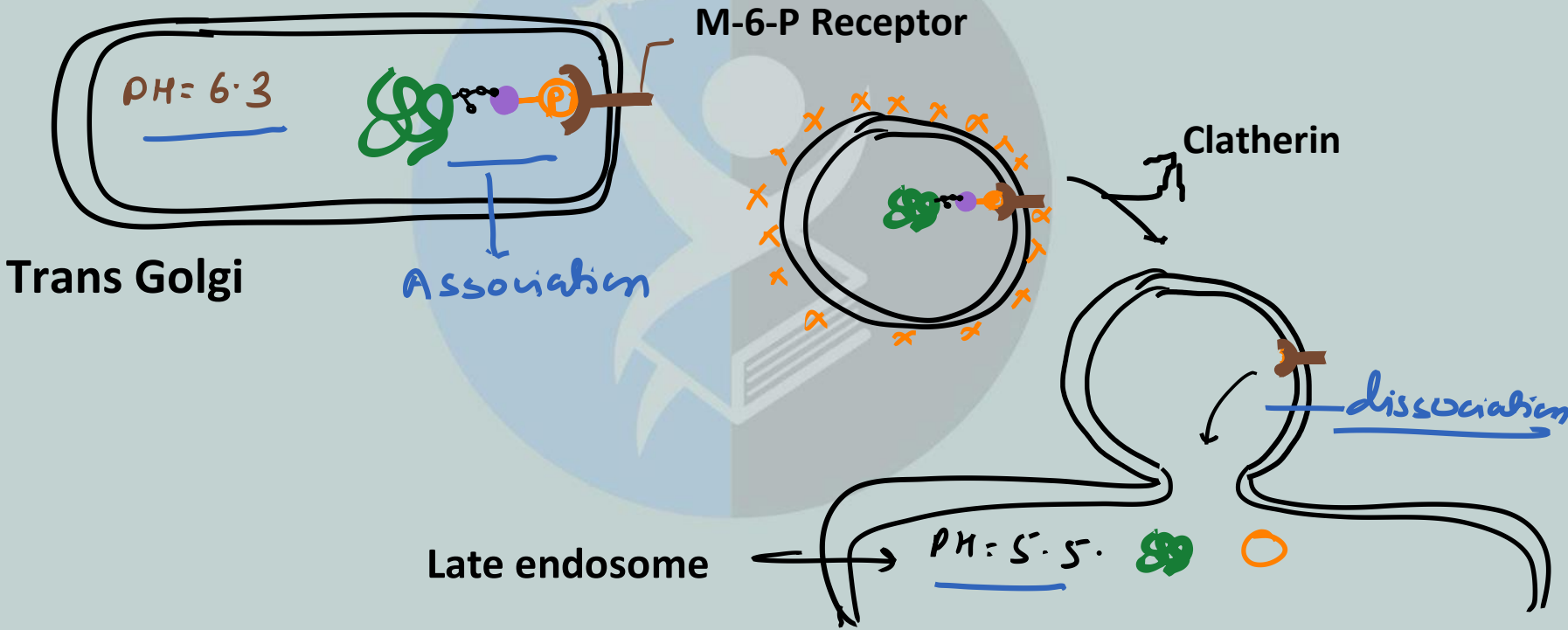
Secretory pathway



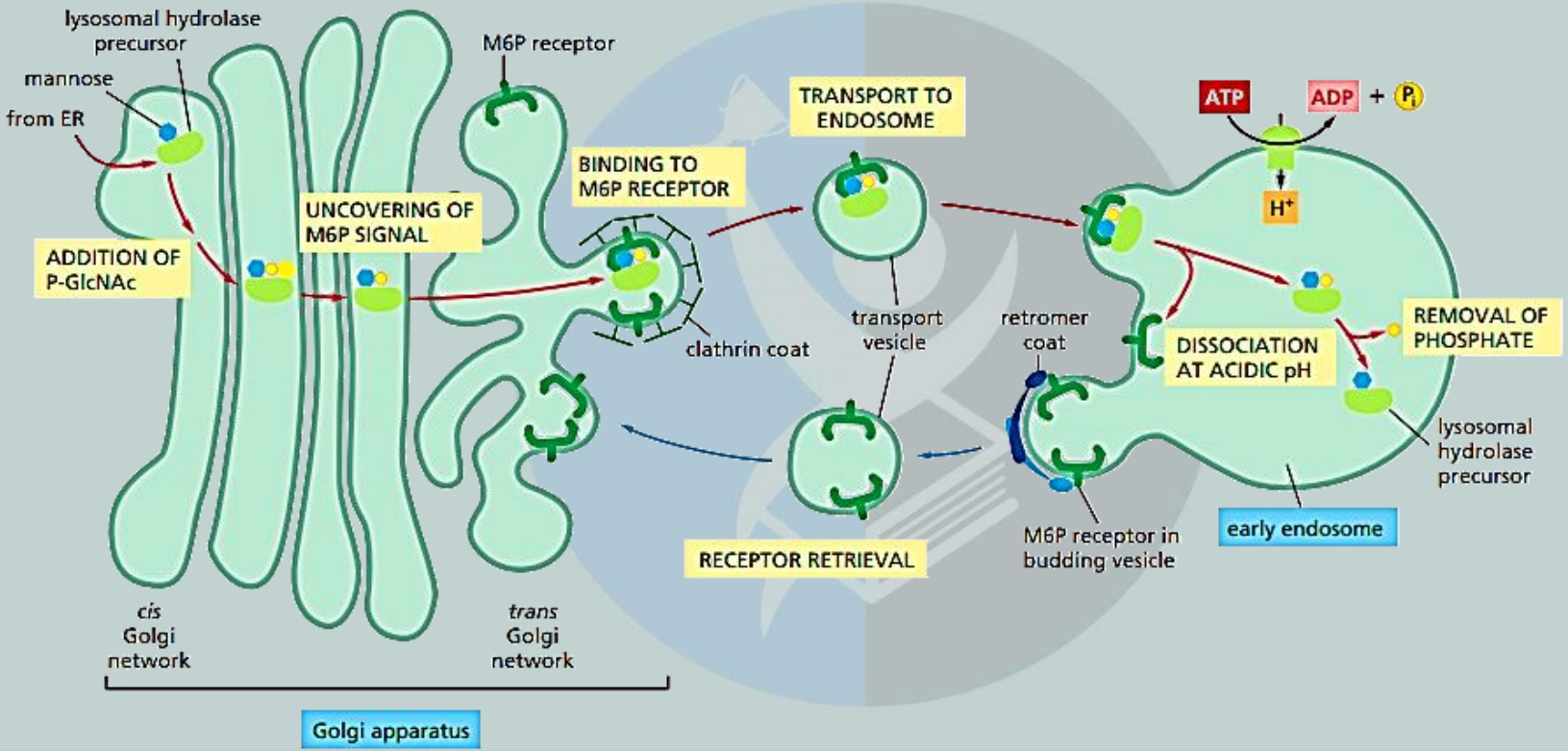

N-linked Glycosylation
Signal patch
Mannose
UDP - N-acetyl Glucosamine
N-acetyl Glucosamine phosphotransferase
UMP
Mannose
Cis - Golgi


NAG
P
NAG
P
mannose-6
P
Trans
Golgi
Median Golgi

M-6-P- Is Recognised By Trans - Golgi (M-6-P Receptor)



Secretory pathway



Late Endosome

Lysosome

- Acid Hydrolase are highly glycosylated
- Very stable
-
- Enzymes are active at low pH (4.5-5)

Functions of golgi

Major center for glycosyslation

- Glycosyl transferase
- Lucan synthase
- NAG- Transferase
- Site for O- linked glycosylation

Ser/Thr

OH

Secretory pathway

- O- Linked glycosylation is multistep process
- Process of N – Linked glycosylation
- Synthesis of glycolipid (sphingolipid)

- Biosynthesis of Carbohydrates of plants

cell wall

- Pectin, Hemicellulose
- Expect- cellulose
- Synthesis on plasma membrane

Question -1

Sar – 1 GTP

Mutation – loss its GTPase actvity

- Cop II vesicle contineous form
- Fusion does not occurs
- Golgi shrinks and eventually disappear

Note - GTP is required for coat formation
GDP triggers coat disassembly

Question -2

signal peptide - toward N terminus of a secretory protein for ER co – translational targeting

Necessary and sufficient

Que Signal Peptide - toward N-Terminus of Secretory Protein for ER - Co Translational Targeting →

✗ (A) . Necessary

(B) . Necessary & Sufficient

- Add Signal Peptide toward N-Terminus of any protein - Can leads → Co-Translational Targeting

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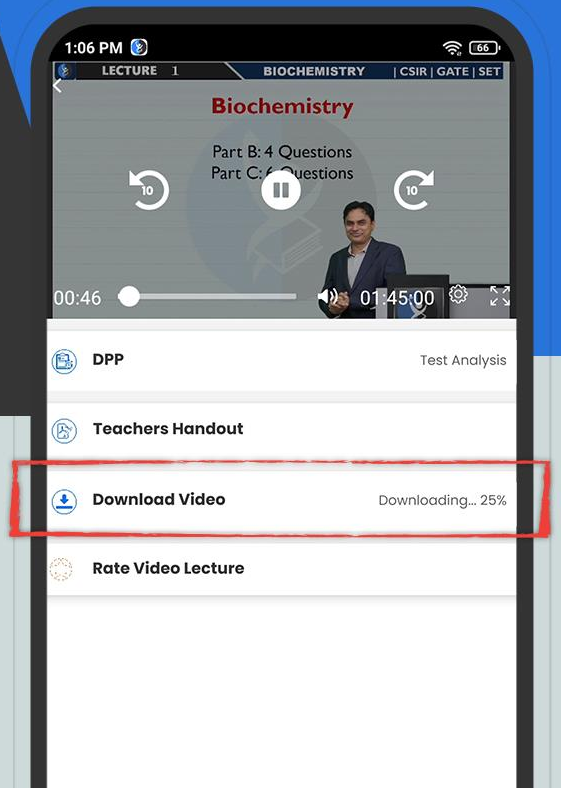

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